

U.S. Army Center for Health Promotion
and Preventive Medicine

**Wildlife Toxicity Assessment for
Propylene**

JUNE 2004

**Prepared by
Health Effects Research Program
Environmental Health Risk Assessment Program**

**USACHPPM Document No: 39-EJ-1138-01N
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**FINAL REPORT
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Acknowledgements

Key Technical Authors:	Christopher J. Salice, Ph.D.	USACHPPM
	George Holdsworth, Ph.D.	T N & Associates 124 S. Jefferson Circle Oak Ridge, TN 37830
	Heidi I. Paulus, B.S.	Oak Ridge Institute of Science and Education, Oak Ridge, TN
Contributors:	Michael J. Quinn, Jr., Ph.D.	Oak Ridge Institute of Science and Education, Oak Ridge, TN
Outside Reviewers:	Gregg Linder, Ph.D.	USGS/BRD/CERC
	John Newsted, Ph.D.	Entrix, Inc.
	Steve Sheffield, Ph.D.	

Point of Contact

For further information or assistance contact the following:

Mark S. Johnson, Ph.D., D.A.B.T.
U.S. Army Center for Health Promotion and Preventive Medicine
Toxicology Directorate: Health Effects Research Program
ATTN: MCHB-TS-THE, Bldg. E2100
Aberdeen Proving Ground, MD 21010-5403
(410) 436-3980 / DSN 584-3980
Mark.s.johnson@us.army.mil

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Department of the Army
U.S. Army Center for Health Promotion and Preventive Medicine

Wildlife Toxicity Assessment for Propylene

CAS No. 115-07-1

June 2004

1. Introduction

Propylene is a colorless gas that is produced in vast quantities by the petrochemical industry throughout the developed world. As summarized by the International Agency for Research on Cancer (IARC), industrial output of propylene in the United States topped 10,248 thousand tons in 1992, the demand driven by use of the compound as a chemical intermediate (IARC 1994). In 1994, propylene was ranked seventh among the top 50 domestically produced chemicals (C&En 1995). Propylene serves as a monomer for the production of polypropylene and as a substrate for important industrial chemicals such as acrylonitrile, propylene oxide, propylene glycol, isopropanol, and is used in the production of synthetic rubber and as a propellant or component in aerosols. Propylene is produced as a by-product of petroleum refining and of ethylene production by steam-cracking of hydrocarbon feedstocks. The compound is released to the environment as a consequence of widespread production and use. Propylene is also released in automobile exhausts and tobacco smoke. The compound has also been identified in emissions from vegetation and combustion of organic matter.

This Wildlife Toxicity Assessment summarizes current knowledge of the toxicological impacts of propylene on wildlife. Evaluating the toxicity of the compound contributes to the derivation of toxicity reference values (TRVs) that serve as screening-level benchmarks for wildlife inhabiting contaminated sites. The protocol for the performance of this assessment is documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. Toxicity Profile

2.1 Literature Review

Relevant biomedical, toxicological, and ecological databases were electronically searched April 20, 2001, and May 2, 2001, using Dialog to identify primary reports of studies and reviews on the toxicology of propylene. Separate searches were carried out linking the compound to mammals, birds, and reptiles and amphibians (combined). In general, a two-tiered approach was used in which all citations were first

evaluated as titles and “key words in context.” All available abstracts of those articles selected in the first tier as possibly relevant to TRV development were then further evaluated for relevancy in the second tier. For propylene, 19 articles were marked for retrieval from 454 initial hits, a disparity arising because the initial sweep captured a substantial number of reports of studies that featured the use of "propylene" as part of the name of a large number of other compounds. These were eliminated in Tier 2 of the selection process. Details of the search strategies and the results of each are documented in Appendix A.

In addition to Dialog searches, a number of U.S. Army reports were identified in the Defense Technical Information Center (DTIC). Secondary references and sources of information on propylene included the National Library of Medicine’s Hazardous Substances Databank (HSDB 2001) and IARC monographs (IARC 1979, 1994).

2.2 Environmental Fate and Transport

Propylene is an ever-present component of the atmosphere, with concentrations reaching $8.2 \mu\text{g}/\text{m}^3$ at remote sites. However, concentrations can range from greater than $150 \mu\text{g}/\text{m}^3$ in urban centers, largely as a result of emissions from automobile exhausts, chemical plants, and various other industrial facilities (HSDB 2001). Propylene has been detected in marine and fresh waters in trace amounts: up to 9.3×10^{-7} ml/l in marine waters and $0.5 \text{ mg}/\text{l}$ in fresh waters (HSDB 2001). Since propylene is not lipophilic, bioaccumulation is unlikely. IARC (1994) reported that 92 companies worldwide, 24 of which are located in the United States, produce propylene.

Volatilization of soil-borne propylene is likely, based on a high vapor pressure of 8.7×10^3 and a Henry's Law constant of $2.0 \times 10^{-1} \text{ atm}\cdot\text{m}^3/\text{mole}$ at 25°C (HSDB 2001). As listed in Table 1, these and other physical-chemical characteristics also favor volatilization of propylene from the surface of marine and freshwater bodies.

Table 1. Summary of Physical-Chemical Properties of Propylene

CAS No.	115-07-1
Molecular weight	42.08
Color	None
Physical state	Gas
Melting point	-185.2°C
Boiling point	-47.4°C
Odor	Slight
Solubility in water	446 mg/L at $20\text{--}25^\circ\text{C}$: soluble in ethanol, diethyl ether

Table 1. Summary of Physical-Chemical Properties of Propylene

Partition coefficients:	
Log K_{ow}	1.77
Log K_{oc}	2.34–2.7
Vapor pressure at 25 °C	8.7×10^3 mm Hg
Henry's Law constant at 25 °C	2.0×10^{-1} atm.m ³ /mole
Conversion factors	1 ppm = 1.72 mg/m ³
	1 mg/m ³ = 0.58 ppm

Sources: HSDB (2001), IARC (1994)

HSDB (2001) discusses the terrestrial fate of propylene in the context of possible degradation by abiotic or biotic processes. For example, the 1,2-epoxide is a possible oxidative derivative of propylene although the extent of its abiotic formation in aqueous media is unclear. Aqueous concentrations of propylene are more likely to be degraded by microorganisms.

A number of mechanisms have been suggested for how the chemical is degraded in the atmosphere. For example, the compound is expected to degrade rapidly in the atmosphere as it reacts with photochemically produced hydroxyl radicals. This process has a half-life of about 14.6 hours (HSDB 2001). Nitrate radicals and ozone will also bring about propylene degradation, although at a slower rate.

2.3 Summary of Mammalian Toxicity

2.3.1 Mammalian Toxicity - Oral

Given the gaseous nature of propylene at ambient temperatures and pressures, there are no data on the toxicological effects of propylene when administered via the oral route.

2.3.1.1 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

Not applicable.

2.3.2 Mammalian Inhalation Toxicity

2.3.2.1 Mammalian Inhalation Toxicity – Acute

A short term (minutes) acute toxic effect to cats was reported in HSDB (2001), where cats were exposed to propylene/air mixtures of up to 800,000 ppm (80%). No effects were observed at concentrations up to 31%, where there was an increase in the severity of effects as concentrations increased to 80%. The pharmacological effects that were observed included: decreased blood pressure, rapid pulse, and the onset of an unusual ventricular ectopic beat. Equivalent concentrations induce deep

anesthesia in rats. Due to the apparent tolerance to high concentrations of propylene in animals, a reliable compound-specific median lethal concentration (LC₅₀) is unavailable.

Although there are few if any toxicological consequences of exposure to propylene via inhalation, the ability of the compound or its metabolites to react with biological macromolecules has been demonstrated. For example, Eide et al. (1995) exposed male Sprague-Dawley rats to propylene (one of a range of alkenes under investigation) at 300 ppm for 12 hours/day on three separate days. Exposure took place in conically-shaped steel inhalation chambers with glass doors and walls. At termination, aliquots of blood and pieces of lung, brain, liver, kidney, and peripheral fat were measured for propylene, and the formation of DNA adducts in liver and lymphocytes was monitored using the ³²P-postlabelling technique. The formation of alkene-hemoglobin adducts was detected using gas chromatography/mass spectrometry. N- (2-hydroxyalkyl) valine adducts of hemoglobin and 7-alkylguanine adducts of DNA were detected consistently in these experiments, including N- (2-hydroxypropyl) valine and 7-propylguanine when propylene was used as the test compound. Earlier, Svensson and Osterman-Golkar (1984) had investigated the formation of hydroxyalkyl derivatives of hemoglobin and DNA when male CBA mice were exposed acutely to either ¹⁴C propylene or ¹⁴C ethylene. ¹⁴C propylene was dissolved in a buffered saline and animals were exposed in an unspecified chamber. Exposure to ¹⁴C ethylene took place in an 11-liter glass chamber. They used the structural homology and the similarity in their reaction products of the two substrates to infer that the reactive intermediate of propylene was propylene oxide. Propylene oxide was subsequently detected in the blood of male F-344 rats exposed in groups of eight to 6 or 600-ppm propylene for either 80 or 480 minutes (Maples and Dahl 1991). Svensson et al. (1991), in an acute toxicity study, administered ¹⁴C propylene to male CBA mice, confirming that propylene oxide was the primary metabolic product of propylene. However, propylene oxide was 6–10 times less effective than ethylene oxide in forming hydroxyalkyl adducts.

Propylene was 1 of 19 hydrocarbon vapors that were administered to male F344 rats via inhalation (nose only) to quantify the rate of uptake (Dahl et al. 1988). Animals were exposed for 80 minutes on 5 separate days to an escalating concentration rate as follows: day 1, 1 ppm; day 2, 5 ppm; day 3, 20 ppm; day 4, 100 ppm; and day 5, 500 ppm. Uptake was determined by linking the vapor concentration and applied flow rate to the amounts of inhaled and exhaled propylene measured in real time, then normalized to the body weight of the animal, and the vapor concentration. Values between 1.3 and 1.9 nmoles/kg/min/ppm were obtained for propylene.

2.3.2.2 Mammalian Inhalation Toxicity – Subacute

The National Toxicology Program (NTP) sponsored a full-scale series of toxicological investigations on propylene in which a 14-day experiment served as a range finder for subsequent longer duration

studies (NTP 1985). The subacute portion of the investigation involved exposing five F344/N rats and B6C3F1 mice/sex/group to 0, 625, 1,250, 2,500, 5,000, or 10,000-ppm propylene, 6 hours/day, and 5 days/week for 14 days. Animals were exposed to the compound in unspecified chambers. Animals were examined daily for mortality and clinical signs, and body weights were monitored at the start and end of the experiment. All animals were euthanized and necropsied, with examination of a full suite of organs and tissues. No compound-related differences were observed in survival, growth, behavior, histology or morphology between controls and any of the treated groups.

2.3.2.3 Mammalian Inhalation Toxicity – Subchronic

The subchronic portion of the NTP's investigation of propylene featured the administration of 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm propylene to 10 F344/N rats and B6C3F1 mice, 6 hours/day, 5 days/week for 14 weeks (NTP 1985). Animals were exposed to the compound in stainless steel and glass chambers. Animals were observed daily for mortality and clinical signs. Body weights were monitored at the start of the experiment and at weekly intervals. Necropsies were carried out on all animals at the end of the experiment, with samples of a full range of tissues and organs from animals that died before the end of the study, all controls, and all members of high dose groups examined histologically. Both test species showed no significant differences in survival, body weight, or behavior, and no compound-related effects in pathology or histopathology were observed.

2.3.2.4 Mammalian Inhalation Toxicity – Chronic

The chronic portion of the NTP study incorporated the exposure of 50 F344/N rats and 50 B6C3F1 mice/sex/group to 0, 5,000, or 10,000 ppm propylene for 24 months (NTP 1985, Quest et al. 1984). All subjects were monitored regularly for survival, clinical signs, and body weight, and a complete necropsy and histopathological examination were carried out on all subjects. In rats, there were no compound-related effects on survival, clinical signs, or body weights, no changes in gross morphology in any tissues or organs, and no obvious compound-related histopathological findings. There were some instances of inflammation of the lining of the nasal cavity. Males and females at 5000ppm showed increased incidence of squamous metaplasia although this was seen only in females at 1000ppm. Females also showed significantly higher epithelial hyperplasia at 10000ppm while males had significantly more nasal inflammation at 5000ppm. Together these results indicate that some effects on the nasal passage are probable but the lack of correlation to dose suggests a tenuous relationship.

Although not statistically significant, high dose male mice displayed a slight but consistently smaller weight-gain than did controls. Survival was near identical to controls if not better in some treatment groups. Treated mice displayed isolated and sporadic instances of some non-neoplastic lesions, including focal inflammation of the kidney. However, the incidence of these lesions, while greater in test animals

than controls (0/50 in males, 1/50 in females), was essentially sporadic and not obviously related to exposure concentration (17/49 in low dose males, 9/49 in high dose males; 7/49 in low dose females, 6/49 in high dose females). The incidence of other non-neoplastic and neoplastic lesions among the groups showed similar low incidences and sporadic distributions with, in some cases, an apparent negative trend with increasing concentration. These data suggest an overall benign nature of the toxicological effects of propylene in the animals tested and do not allow the derivation of a plausible No-Observed-Adverse-Effect-Level (NOAEL) relevant to TRV development.

Ciliberti et al. (1988) exposed 100–120 Sprague-Dawley rats/sex/group and Swiss mice/sex/group to 0, 200, 1,000, or 5,000-ppm propylene, 7 hours/day, 5 days/week for 78 weeks, and published data that are consistent with the negative findings of the NTP study on propylene. Exposure took place in a stainless steel chamber with glass doors (Ciliberti et al. 1988). Clinical signs were examined three times a week, body weights were monitored every 2 weeks, and all animals were subjected to a gross examination at the time of weighing. All animals were maintained until they died naturally, at which point they were necropsied and samples of organs and tissues were examined histopathologically. The reported results of this investigation focused on the formation of neoplasms, the incidences of which appeared to be similar to controls at all exposure levels. No findings relating to the formation of non-neoplastic lesions were reported.

2.3.2.5 Studies Relevant for Mammalian TRV Development for Inhalation Exposures

The capacity of propylene to induce anesthesia, with full recovery of faculties on cessation of exposure, is consistent with the negative toxicological results outlined in Sections 2.3.2.1-2.3.2.4. Overall, the results suggest a relatively benign nature of propylene in biological systems and argue against the likelihood that a viable TRV for propylene can be derived from the toxicological information that is available. However, the formation of 2-hydroxypropyl derivatives of hemoglobin and guanine indicates that propylene has biochemical activity, most likely through its propylene oxide intermediate. In contrast to ethylene, there have been no studies on the kinetics of propylene oxide formation from propylene. However, it is reasonable to speculate that, similar to ethylene oxide formation from ethylene (Bolt 1998), the rate of formation of propylene oxide from propylene may saturate below the toxicity threshold for the former substance. This would explain the benign effects of propylene when compared to the more severe effects of its metabolic product.

2.3.3 Mammalian Inhalation Toxicity – Other

Propylene has been included in two surveys on the genotoxicity of environmentally important compounds with negative findings. Ambiguous results were obtained from the compound in a modified version of the L5178Y mouse lymphoma forward mutation assay (McGregor et al. 1991). Additionally,

the compound was negative for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster* (Foureman et al. 1994).

2.3.4 Mammalian Dermal Toxicity

No data are available.

2.4 Summary of Avian Toxicology

No toxicological data for the effects of propylene on avian species was located. Ecotoxicological research on the effects of this compound on birds is recommended.

2.5 Amphibian Toxicology

No toxicological data for the effects of propylene on amphibian species was located. Ecotoxicological research on the effects of this compound on amphibians is recommended.

2.6 Reptilian Toxicology

No toxicological data for the effects of propylene on reptiles was located. Ecotoxicological research on the effects of this compound on reptiles is recommended.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Values for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

At this time it is not possible to derive a TRV for the oral route of exposure for propylene. Due to the gaseous nature of the compound, it cannot be administered orally.

3.1.2 TRVs for Inhalation Exposures for the Class Mammalia

The data that has been obtained from the inhalation studies presented in this document indicated that propylene is not toxic at the levels tested. It was reported in NTP (1985) that even at concentrations of 10,000-ppm inhalation for 2 years, there was little toxicological consequence. Further need for studies characterizing the toxicity of propylene is evident given that propylene is present in the environment in large quantities.

4. IMPORTANT RESEARCH NEEDS

The limited availability of data on the toxicity of propylene to wildlife species precludes the development of a TRV. Hence, more studies of the compound and its derivatives are recommended. In particular, chronic toxicity studies on non-mammalian wildlife such as birds, reptiles and amphibians are particularly warranted. The main challenge appears to lie in finding levels of propylene that result in toxicity to study organisms.

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1. APPENDIX A

LITERATURE REVIEW

Separate searches in DIALOG were carried out on propylene on April 20, 2001, and on May 2, 2001.

In the first search the following files were scanned:

File 155 MEDLINE, File 156 TOXLINE, File 5 BIOSIS, File 10 AGRICOLA, File 203 AGRIS, File 399 Chemical Abstracts, File 77 Conference Papers Index, File 35 Dissertation Abstracts, File 40 ENVIRONMENTAL, File 68 Environmental Bibliography, File 76 Life Sciences Collection, File 41 Pollution Abstracts, File 185 Zoological Record, File 6 NTIS, File 50 CAB, File 144 PASCAL, File 34 SCISEARCH, and File 434 SCISEARCH.

The search strategy for **Amphibians & Reptiles**:

- ◆ Chemical name, CAS numbers
- ◆ AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT glycol
- ◆ RD (reduce duplicates)
- ◆ NOT dibromide
- ◆ NOT dichloride
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)

The search strategy for **Birds**:

- ◆ Chemical name, CAS numbers
- ◆ AND chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus()domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)

- ◆ RD (reduce duplicates)
- ◆ NOT dibromide or dichloride

- ◆ NOT dibromide

- ◆ NOT dichloride

The search strategy for **Laboratory Mammals:**

- ◆ Chemical name, CAS numbers

- ◆ AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)

- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))

- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)/ti,de

- ◆ NOT (meeting()poster)

- ◆ NOT (meeting()abstract)

- ◆ NOT (Conference()proceeding?)

- ◆ RD (reduce duplicates)

- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)

- ◆ NOT (glycols or polymer or poly or tetraacetic or tetraacetate or dichlorides)

- ◆ NOT EDTA

- ◆ NOT (Dimethanesulphonate? or dimethanesulfonate? or diamine? or EDS)

- ◆ AND LA=English

The search strategy for **Wild Mammals:**

- ◆ Chemical name, CAS numbers

- ◆ And (didelphidae or opossum? or sorcidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae) or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or mycogastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?

- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)/ti,de
- ◆ NOT (Meeting()Poster?)
- ◆ NOT (Meeting()Abstract?)
- ◆ NOT (Conference()Proceedings?)
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women? or men? or occupational?)
- ◆ RD
- ◆ NOT steriliz?
- ◆ NOT oxide

When the search retrieved an appreciable number of hits, *keywords in context* were reviewed to minimize costs before any abstracts were downloaded (Tier 1). However, when only a limited number of studies were identified by the search, the abstracts were downloaded at the time of the search (Tier 2).

The second search examined File 155 Medline, File 156 Toxline, File 535 Thomas Register Online, File 76 Life Sciences Collection, File 185 Zoological Record Online, and File 5 Biosis Reviews and had the following structure:

For Laboratory Animals

- ◆ CAS. Number
- ◆ AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (Reduce Duplicates)

For Birds

- ◆ CAS. Number

- ◆ AND chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus()domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl)
- ◆ RD (Reduce Duplicates)

For **Wild Mammals**

- ◆ CAS. Number
- ◆ And (didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae) or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or myocastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?
- ◆ RD (Reduce Duplicates)

For **Amphibians/Reptiles**

- ◆ CAS. Number
- ◆ AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- ◆ RD (Reduce Duplicates)

As noted in Section 2.1, 454 hits on propylene were obtained in the initial searches, of which 19 were selected for retrieval.